

ORIGINAL

Application Based on

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COMPOUNDS AND SYNTHESIS PROCESS

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COMPOUNDS AND SYNTHESIS PROCESS

FIELD OF THE INVENTION

This invention relates to 6-chlorophenolic compounds bearing two
5 amino substituents, and a process for synthesizing such compounds using a 2-
alkyl-6-aminobenzoxazole to form a 2-alkyl-6-amino-7-chlorobenzoxazole in
which the 2-alkyl group is unbranched at the α carbon.

BACKGROUND OF THE INVENTION

10 Phenolic compounds are useful for the synthesis of useful organic
compounds such as couplers for colorant uses. Useful compounds include those
having a substituted first amino group in the 2-position and a substituted second
amino group in another position such as the 5-position of the phenol. One
example of such useful compounds is a phenolic coupler useful as a cyan dye-
15 forming coupler in a silver halide imaging process. Particularly useful phenolic
compounds, which give the desired hue and absorption curve shape, are those
containing the requisite two amino groups, including a ballast in one of the two
groups, and a 6-chloro substituent. A ballast is a hydrophobic group having 8 or
more aliphatic carbon atoms which serves to keep the coupler and resulting dye
20 within the hydrophobic dispersion in which it is present so that it will not be
washed out during the aqueous processes associated with development.

There have been available several processes for obtaining phenolic
compounds bearing two amino substituents. In the first, a phenol is provided with
an amine group in the 2- position and a nitro group in the other desired amino
25 position. The 2-position is converted to the desired amino substituent using acid
chloride. Then, the nitro group is reduced to amine and the second amine group is
converted to the desired amino substituent using acid chloride. This method is
limited in the order of introducing the amino substituents and methods for
introducing the 6-chloro substituent. Further, it would be desirable to avoid the
30 use of nitroaminophenol compounds for safety reasons since such materials
present an explosion concern.

Another method is described in Begley, U.S. 6,201,125. The use of 2-alkyl-6-nitrobenzoxazoles is suggested to prepare 2,5-dicarbonamido phenols, but there is no indication of how to prepare the desired 6-chloro-2,5-dicarbonamido phenols.

5 In yet another method as described by Mitsunori Ono in "Heterocycles", 27(4), 881, (1988). The use of 2-alkyl-6-nitrobenzoxazoles is suggested to prepare 2,5-dicarbonamido phenols but again there is no indication of how to prepare 6-chloro-2,5-dicarbonamido phenols. In addition, the examples employ a 2-t-butyl group, and it was found that an attempt to hydrolyze the
10 oxazole ring in acid to unblock the 2-position was unsatisfactory and "all attempted usual acid cleavage...failed." Ono is ultimately concerned with effecting a reaction at the 4-position of the phenol ring rather than effecting a conversion of the nitro group or introduction of a chloro group, so the use of alkaline KOH hydrolysis is of no concern. But if one does desire to convert the
15 nitro group, as in the present case, there is a major concern, because the use of alkaline KOH unblocking will also initiate undesired side reactions at the converted nitro site.

 It is desirable to develop a process that provides a simple and safe way to prepare 6-chloro-2,5-dicarbonamido phenol compounds in good yield.

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SUMMARY OF THE INVENTION

 The invention provides a process for synthesizing 6-chloro-2,5-dicarbonamido phenol compounds comprising a step employing a 2-alkyl-6-aminobenzoxazole to form a 2-alkyl-6-amino-7-chlorobenzoxazole in which the
25 2-alkyl group is unbranched at the α carbon. It also provides intermediate compounds useful in the process.

 The process and intermediates provide a simple and safe way to prepare 6-chloro-2,5-dicarbonamido phenol compounds in good yield.

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DETAILED DESCRIPTION OF THE INVENTION

 The process of the invention is generally as described above. It is a process for synthesizing 6-chloro-2,5-dicarbonamido phenol compounds

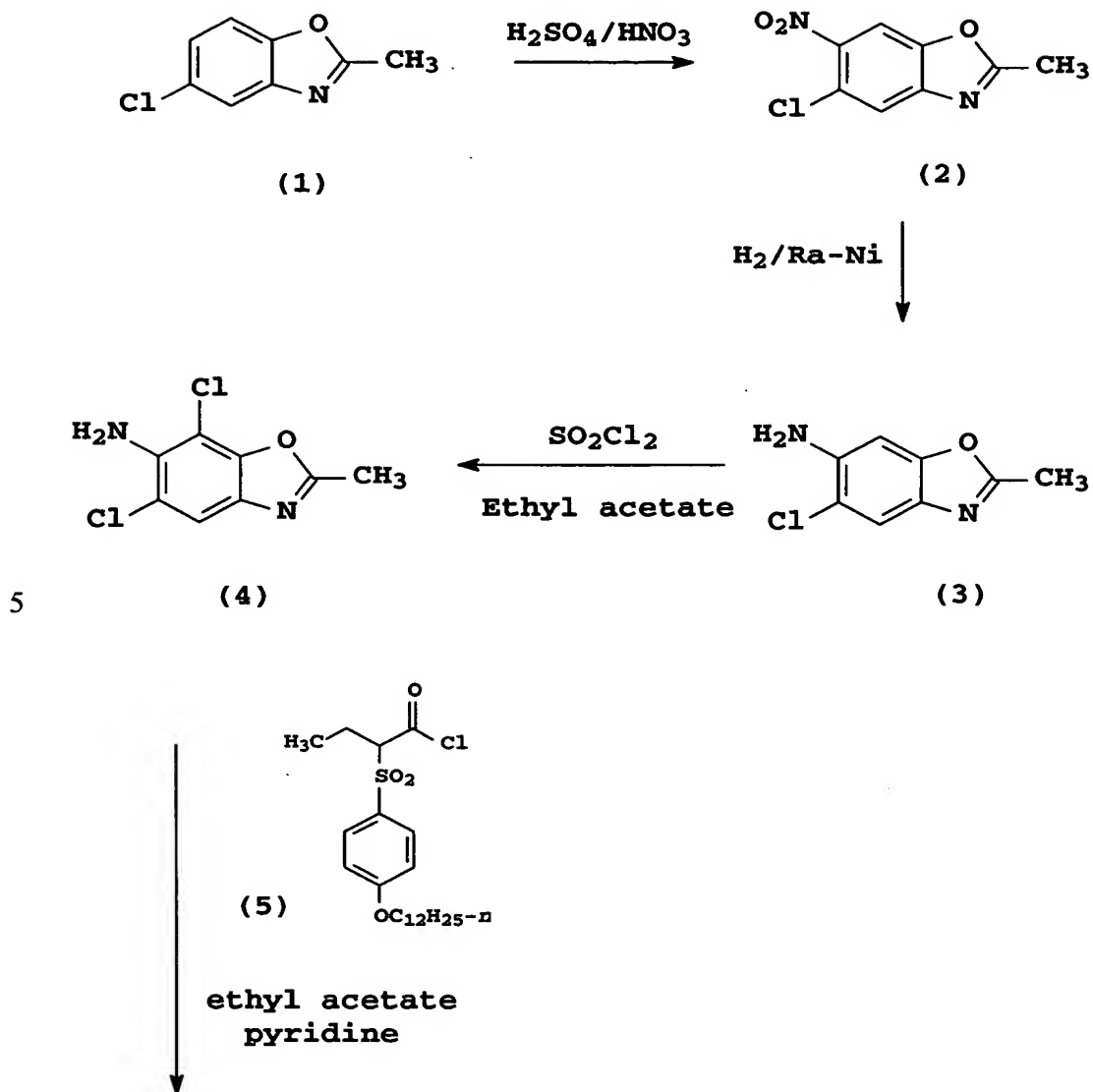
comprising a step employing a 2-alkyl-6-aminobenzoxazole to form a 2-alkyl-6-amino-7-chlorobenzoxazole in which the 2-alkyl group is unbranched at the α carbon.

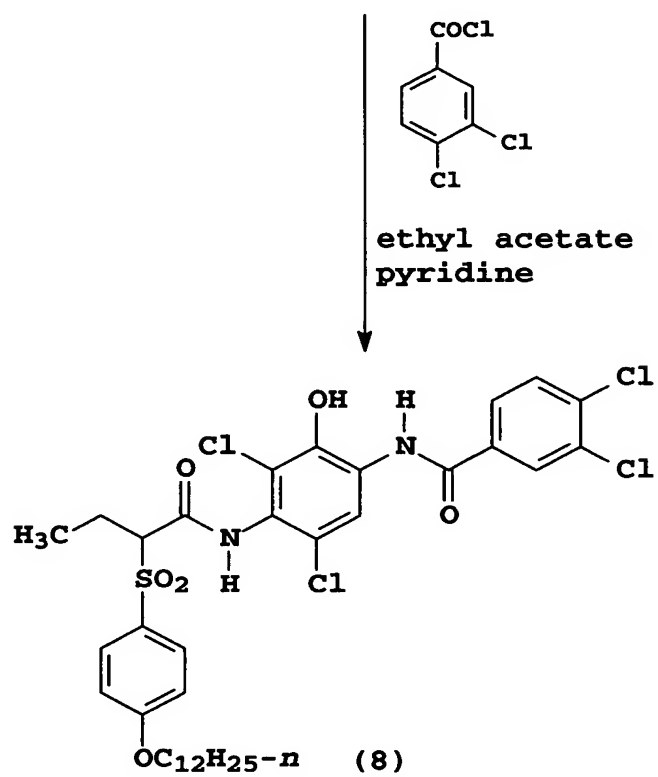
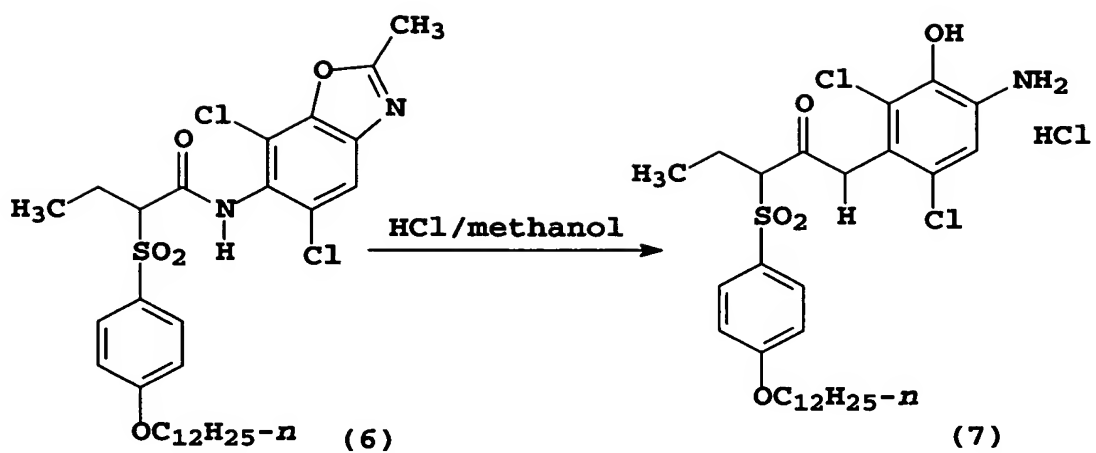
5 The starting 2-alkyl-5-chlorobenzoxazole or 2-alkyl-5-fluorobenzoxazole materials are readily available from The Aldrich Chemical Company of Milwaukee WI, or can be made from 2-aminophenol upon reaction with a suitable acylating agent. The process entails nitrating the starting material to form a 2-alkyl-5-chloro-6-nitrobenzoxazole or 2-alkyl-5-fluoro-6-nitrobenzoxazole. The next step is to reduce the nitro group to the amine using
10 any known method such as hydrogen plus a transition metal catalyst like Raney nickel. The next step is to introduce the 7-chloro substituent into the benzoxazole ring using any known chlorination method such as N-chlorosuccinimide or sulfuryl chloride. The resulting 2-alkyl-6-amino-5,7-dichlorobenzoxazole or 2-alkyl-6-amino-7-chloro-5-fluorobenzoxazole is then reacted to replace one of the
15 amine hydrogen atoms such as by reaction with an acid chloride, including an alkyl, aryl or heterocyclic acid chloride. Appended reaction sites on the resulting carbonamide group may undergo further reactions such as the reaction of an electrophile or nucleophile.

20 Next, the oxazole is unblocked through acid hydrolysis to convert the compound into a 2-amino-5-carbonamido-6-chlorophenol. Now the 2-amino group is reacted with an acid chloride in the same manner as for the 5-position (but usually a different acid chloride compound is used.) The end result is the desired 6-chloro-2,5-dicarbonamidophenol.

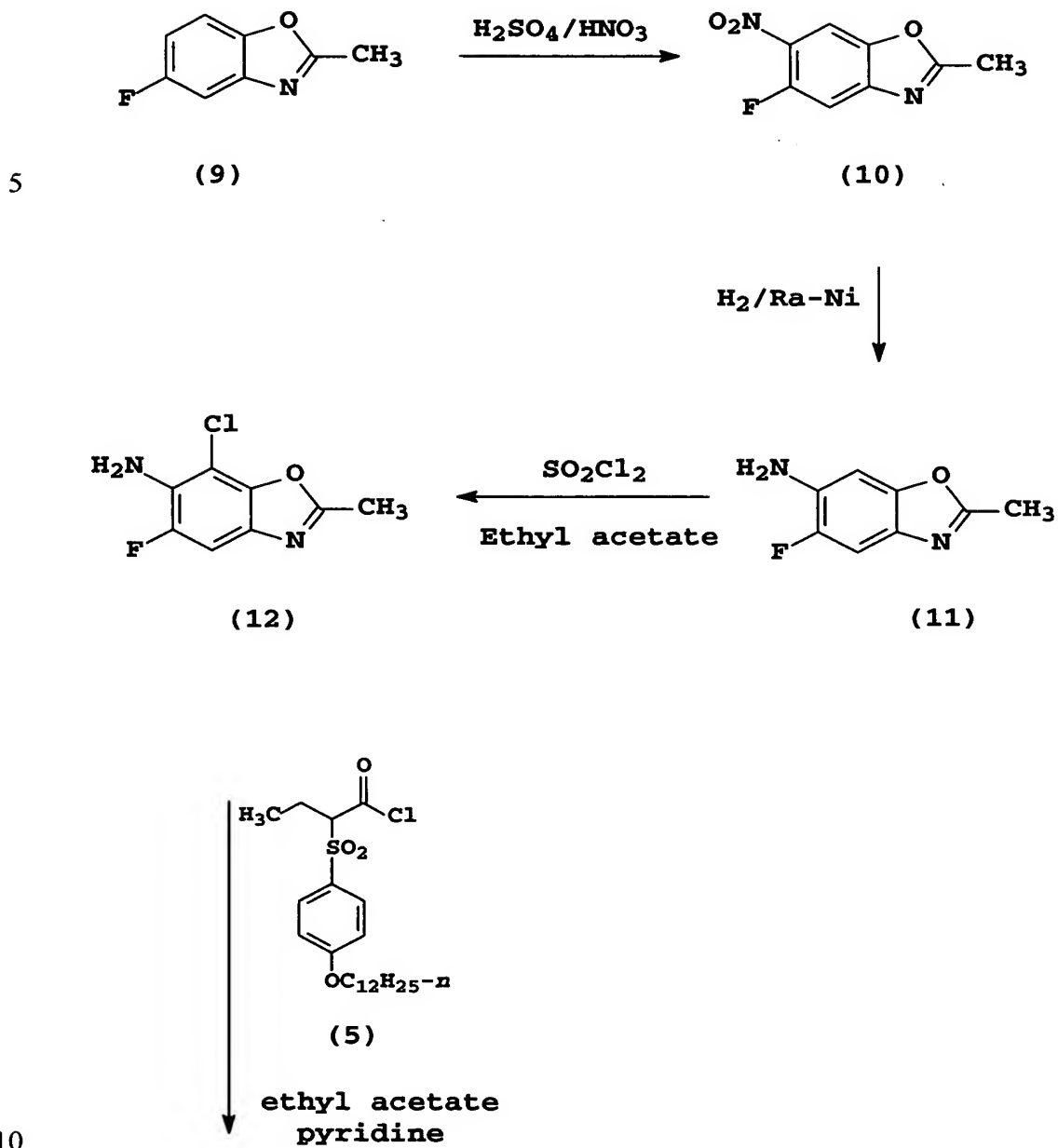
25 The invention is exemplified in Schemes 1 and 2 for the preparation of Compounds 8 and 15:

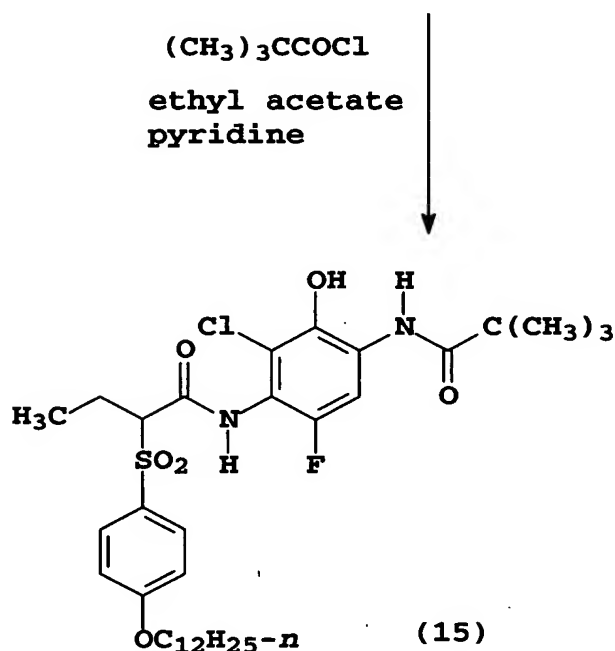
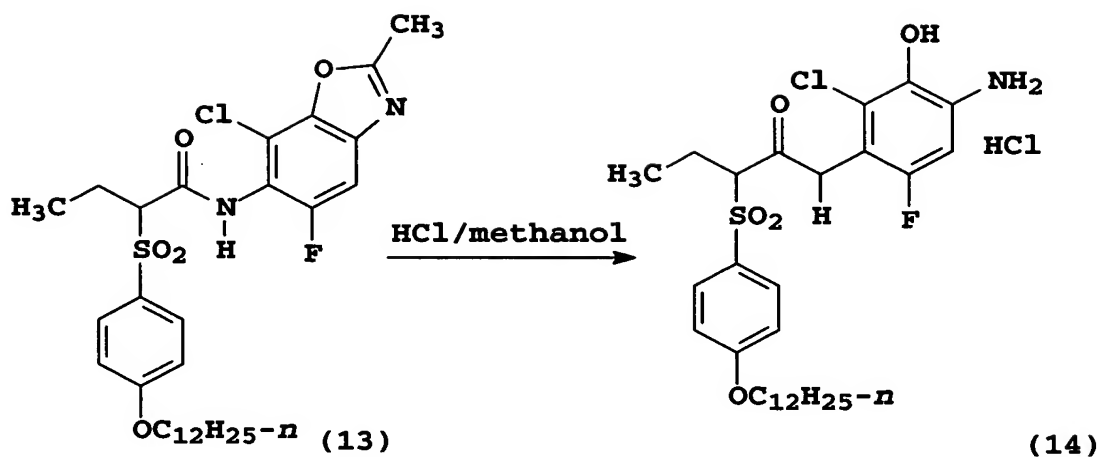
Scheme 1





Scheme 2





5 5-Chloro-2-Methyl-6-Nitrobenzoxazole (2).

Concentrated sulfuric acid (150mL) was stirred mechanically and cooled in an ice/water bath. To this was gradually added 5-chloro-2-methylbenzoxazole (1), (75g, 0.45 Moles), at such a rate that the temperature stayed at 30°C, over a 15-20 minute period. A solution of concentrated sulfuric acid (40mL), and concentrated nitric acid (32mL), was prepared and added drop by drop to the benzoxazole solution at such a rate that the temperature was maintained at approximately 20°C. When this acid solution had been added the cooling bath was removed and

the mixture allowed to stir at room temperature for 1 hour. At the end of this period the solution was carefully poured onto ice with good stirring. Sufficient water was then added to get good mixing. The solid was filtered off, washed well with water followed by methanol and finally air dried. Yield 90.6g

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6-Amino-5-Chloro-2-Methylbenzoxazole (3).

5-Chloro-2-methyl-6-nitrobenzoxazole (30g), was dissolved in tetrahydrofuran (150mL), and Raney-Nickel which had been pre-washed with water (x3) and tetrahydrofuran (x3), was added. The mixture was then hydrogenated at room
10 temperature and 50psi of hydrogen. The reaction is complete in approximately 1.5 hours. After this period, the catalyst is filtered off and the solution concentrated under reduced pressure. The residue is triturated with heptane, cooled and the solid filtered off. Yield 22g.

15 6-Amino-5,7-Dichloro-2-Methylbenzoxazole (4).

6-Amino-5-chloro-2-methylbenzoxazole (10g, 54.76mMole) was dissolved in ethyl acetate (150mL). At room temperature and with good stirring, sulfuryl chloride (8.8mL, 109.52mMole) was added drop by drop over a 20-minute period. As the addition proceeds, additional ethyl acetate (350mL) was added to keep the
20 mixture stirring. After 1 hour the precipitate was filtered off, washed with ether and air-dried. Yield 10.5g.

2-[(4-Dodecyloxyphenyl)sulfonyl]butanoyl Chloride, (5).

2-[(4-Dodecyloxyphenyl)sulfonyl]butanoic acid (19.5g, 47.33mMole) was
25 suspended in ethyl acetate (150mL) to which was added several drops of dimethylformamide and thionyl chloride (14.4mL, 119mMole). The mixture was heated at 70°C for 1.5 hours, cooled, concentrated under reduced pressure, co-evaporated with ethyl acetate (2x100mL) and the oil so obtained used as such in the next step of the reaction sequence.

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Compound (6).

6-Amino-5,7-dihloro-2-methylbenzoxazole (3), (10.0g, 39.45mMole) was dissolved in tetrahydrofuran (150mL), cooled to approximately 15°C and dry pyridine (7.7mL, 94.66mMole) added. The 2-[(4-

- 5 dodecyloxyphenyl)sulfonyl]butanoyl chloride (47.33mMole), dissolved in ethyl acetate (50mL), was then added to the solution at a fairly fast drip rate over a 15 minute period while maintaining good stirring and keeping the temperature at approximately 15°C. At the end of the addition, the cooling bath was removed and the reaction mixture stirred at room temperature for an additional 15 minutes.
- 10 The reaction mixture was then washed with 2N-HCl (3x200mL), dried (MgSO₄), filtered and concentrated to an oil. The oil was dissolved in 25% ethyl acetate in heptane and subjected to flash chromatography eluting with 25, 30, 40 and finally 50% ethyl acetate in heptane. The second major band was collected to give the product. Yield 7.5g.

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Compound (7).

Compound (6), (7.5g, 12.26mMole) was suspended in methanol (70mL) and tetrahydrofuran (10mL). Concentrated hydrochloric acid (3mL) added and the mixture heated to 65°C for approximately 3 hours. The solution was then cooled

20 and concentrated under reduced pressure until the product began to crystallize. Enough acetonitrile was added to precipitate out the product. The mixture was cooled overnight to 0°C and the product filtered off, washed with diethyl ether and air-dried. Yield 7.5g.

25 Compound (8).

Compound (7) (2.5g, 4.0mMole), was dissolved in tetrahydrofuran (40mL) with gentle heating. Dry pyridine (0.36mL, 4.41mMole) was added followed by the drop by drop addition of 3,4-dichlorobenzoyl chloride (0.92g, 4.41mMole) in tetrahydrofuran (10mL). After the addition the mixture was stirred at room

30 temperature for 30 minutes. The reaction mixture was then diluted with ethyl acetate, washed with 2N-HCl(2x50mL), dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was dissolved in 10% ethyl acetate –

methylene chloride and subjected to flask chromatography eluting with 10% then 15% ethyl acetate – methylene chloride to obtain Compound (8). Yield 2.5g.

5-Fluoro-2-Methyl-6-Nitrobenzoxazole (10).

5 Concentrated sulfuric acid (60mL) was stirred mechanically and cooled in an ice/water bath. To this was gradually added 5-fluoro-2-methylbenzoxazole (9), (20g, 0.132 Moles), at such a rate that the temperature stayed at 15-20°C, over a 15-20 minute period. A solution of concentrated sulfuric acid (11mL), and concentrated nitric acid (10mL), was prepared and added drop by drop to the
10 benzoxazole solution at such a rate that the temperature was maintained at approximately 10°C. When this acid solution had been added the cooling bath was removed and the mixture allowed to stir at room temperature for 1 hour. At the end of this period the solution was carefully poured onto ice with good stirring. Sufficient water was then added to get good mixing. The solid was
15 filtered off, washed well with water and air-dried. Yield 16.0g

6-Amino-5-Fluoro-2-Methylbenzoxazole (11).

5-Fluoro-2-methyl-6-nitrobenzoxazole (16g, 81.57mMole), was dissolved in tetrahydrofuran (150mL), and methanol (50mL). Raney-Nickel which had been
20 pre-washed with water (x3) and tetrahydrofuran (x3), was added and the mixture was then hydrogenated at room temperature and 50psi of hydrogen. The reaction is complete in approximately 1.5 hours. After this period, the catalyst is filtered off and the solution concentrated under reduced pressure. The residue is triturated with heptane, cooled and the solid filtered off. Yield 12g.

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6-Amino-7-Chloro-5-Fluoro-2-Methylbenzoxazole (12).

6-Amino-5-fluoro-2-methylbenzoxazole (12g, 72.22mMole) was dissolved in ethyl acetate (100mL) containing dry pyridine (5.8mL, 72.22mMole). At room temperature and with good stirring, sulfonyl chloride (7.0mL, 86.66mMole) was
30 added drop by drop over a 20-minute period. After stirring at room temperature for about 30 minutes, the reaction was diluted with ethyl acetate, washed with 2N-HCl, dried (MgSO₄), filtered and concentrated to give a solid. This solid was

dissolved in methylene chloride and passed through a short column of silica gel eluting with methylene chloride to give the product. Yield 5.0g.

2-[(4-Dodecyloxyphenyl)sulfonyl]butanoyl chloride, (5).

- 5 2-[(4-Dodecyloxyphenyl)sulfonyl]butanoic acid (11.1g, 26.92mMole) was suspended in ethyl acetate (100mL) to which was added several drops of dimethylformamide and thionyl chloride (10.0mL, 134.6mMole). The mixture was heated at 70°C for 1.5 hours, cooled, concentrated under reduced pressure, co-evaporated with ethyl acetate (2x100mL) and the oil so obtained used as such
10 in the next step of the reaction sequence.

Compound (13).

- 6-Amino-7-chloro-5-fluoro-2-methylbenzoxazole (12), (4.5g, 22.43mMole) was dissolved in tetrahydrofuran (100mL), cooled to approximately 15°C and dry
15 pyridine (4.3mL, 53.84mMole) added. 2-[(4-Dodecyloxyphenyl)sulfonyl]butanoyl chloride (26.92mMole), was dissolved in ethyl acetate (20mL), was then added to the solution at a fairly fast drip rate over a 15 minute period while maintaining good stirring and keeping the temperature at approximately 15°C. At the end of the addition, the cooling bath was removed
20 and the reaction mixture stirred at room temperature for an additional 15 minutes. The reaction mixture was then washed with 2N-HCl (3x100mL), dried (MgSO₄), filtered and concentrated to an oil. This oil solidified on standing and was used as such in the next step.

25 Compound (14).

- Compound (13), (22.43mMole) was dissolved in methanol (100mL) and concentrated hydrochloric acid (5mL) added. The mixture was heated to 65°C for approximately 3 hours. The solution was then cooled and concentrated under reduced pressure until the product began to crystallize. Enough acetonitrile was
30 added to precipitate out the product. The mixture was cooled overnight to 0°C and the product filtered off, washed with diethyl ether and air-dried. Yield 13.4g.

Compound (15).

Compound (14) (3.0g, 4.94mMole), was dissolved in tetrahydrofuran (40mL) with gentle heating. Dry pyridine (0.96mL, 11.85mMole) was added followed by the drop by drop addition of a solution of pivaloyl chloride (0.7g, 5.92mMole) in tetrahydrofuran (10mL). After the addition the mixture was stirred at room temperature for 30 minutes. The reaction mixture was then diluted with ethyl acetate, washed with 2N-HCl(2x50mL), dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was dissolved in 5% ethyl acetate – methylene chloride and subjected to flask chromatography eluting with 5%, 7.5% and 10% ethyl acetate – methylene chloride to obtain Compound (15). Yield 2.0g.

Unless otherwise specifically stated, use of the term "substituted" or "substituent" means any group or atom other than hydrogen. Additionally, when the term "group" is used, it means that when a substituent group contains a substitutable hydrogen, it is also intended to encompass not only the substituent's unsubstituted form, but also its form further substituted with any substituent group or groups as herein mentioned, so long as the substituent does not destroy properties necessary for photographic utility. Suitably, a substituent group may be halogen or may be bonded to the remainder of the molecule by an atom of carbon, silicon, oxygen, nitrogen, phosphorous, or sulfur. The substituent may be, for example, halogen, such as chlorine, bromine or fluorine; nitro; hydroxyl; cyano; carboxyl; or groups which may be further substituted, such as alkyl, including straight or branched chain or cyclic alkyl, such as methyl, trifluoromethyl, ethyl, *t*-butyl, 3-(2,4-di-*t*-pentylphenoxy) propyl, and tetradecyl; alkenyl, such as ethylene, 2-butene; alkoxy, such as methoxy, ethoxy, propoxy, butoxy, 2-methoxyethoxy, *sec*-butoxy, hexyloxy, 2-ethylhexyloxy, tetradecyloxy, 2-(2,4-di-*t*-pentylphenoxy)ethoxy, and 2-dodecyloxyethoxy; aryl such as phenyl, 4-*t*-butylphenyl, 2,4,6-trimethylphenyl, naphthyl; aryloxy, such as phenoxy, 2-methylphenoxy, alpha- or beta-naphthyloxy, and 4-tolyloxy; carbonamido, such as acetamido, benzamido, butyramido, tetradecanamido, alpha-(2,4-di-*t*-pentyl-phenoxy)acetamido, alpha-(2,4-di-*t*-pentylphenoxy)butyramido, alpha-(3-pentadecylphenoxy)-hexanamido,

alpha-(4-hydroxy-3-*t*-butylphenoxy)-tetradecanamido, 2-oxo-pyrrolidin-1-yl, 2-oxo-5-tetradecylpyrrolin-1-yl, N-methyltetradecanamido, N-succinimido, N-phthalimido, 2,5-dioxo-1-oxazolidinyl, 3-dodecyl-2,5-dioxo-1-imidazolyl, and N-acetyl-N-dodecylamino, ethoxycarbonylamino, phenoxycarbonylamino, 5 benzyloxycarbonylamino, hexadecyloxycarbonylamino, 2,4-di-*t*-butylphenoxy carbonylamino, phenyl carbonylamino, 2,5-(di-*t*-pentylphenyl) carbonylamino, *p*-dodecyl-phenyl carbonylamino, *p*-tolyl carbonylamino, N-methylureido, N,N-dimethylureido, N-methyl-N-dodecylureido, N-hexadecylureido, N,N-dioctadecylureido, N,N-dioctyl-N'-10 ethylureido, N-phenylureido, N,N-diphenylureido, N-phenyl-N-*p*-tolylureido, N-(*m*-hexadecylphenyl)ureido, N,N-(2,5-di-*t*-pentylphenyl)-N'-ethylureido, and *t*-butyl carbonamido; sulfonamido, such as methylsulfonamido, benzenesulfonamido, *p*-tolylsulfonamido, *p*-dodecylbenzenesulfonamido, N-methyltetradecylsulfonamido, N,N-dipropyl-sulfamoylamino, and 15 hexadecylsulfonamido; sulfamoyl, such as N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dipropylsulfamoyl, N-hexadecylsulfamoyl, N,N-dimethylsulfamoyl; N-[3-(dodecyloxy)propyl]sulfamoyl, N-[4-(2,4-di-*t*-pentylphenoxy)butyl]sulfamoyl, N-methyl-N-tetradecylsulfamoyl, and N-dodecylsulfamoyl; carbamoyl, such as N-methylcarbamoyl, N,N-dibutylcarbamoyl, N-octadecylcarbamoyl, N-[4-(2,4-di-20 pentylphenoxy)butyl]carbamoyl, N-methyl-N-tetradecylcarbamoyl, and N,N-dioctylcarbamoyl; acyl, such as acetyl, (2,4-di-*t*-amylphenoxy)acetyl, phenoxycarbonyl, *p*-dodecyloxyphenoxycarbonyl methoxycarbonyl, butoxycarbonyl, tetradecyloxy carbonyl, ethoxycarbonyl, benzyloxycarbonyl, 3-pentadecyloxy carbonyl, and dodecyloxy carbonyl; sulfonyl, such as 25 methoxysulfonyl, octyloxysulfonyl, tetradecyloxysulfonyl, 2-ethylhexyloxysulfonyl, phenoxysulfonyl, 2,4-di-*t*-pentylphenoxysulfonyl, methylsulfonyl, octylsulfonyl, 2-ethylhexylsulfonyl, dodecylsulfonyl, hexadecylsulfonyl, phenylsulfonyl, 4-nonylphenylsulfonyl, and *p*-tolylsulfonyl; sulfonyloxy, such as dodecylsulfonyloxy, and hexadecylsulfonyloxy; sulfinyl, 30 such as methylsulfinyl, octylsulfinyl, 2-ethylhexylsulfinyl, dodecylsulfinyl, hexadecylsulfinyl, phenylsulfinyl, 4-nonylphenylsulfinyl, and *p*-tolylsulfinyl; thio, such as ethylthio, octylthio, benzylthio, tetradecylthio, 2-(2,4-di-*t*-

pentylphenoxy)ethylthio, phenylthio, 2-butoxy-5-t-octylphenylthio, and *p*-tolylthio; acyloxy, such as acetyloxy, benzoyloxy, octadecanoyloxy, *p*-dodecylamidobenzoyloxy, N-phenylcarbamoyloxy, N-ethylcarbamoyloxy, and cyclohexylcarbonyloxy; amine, such as phenylanilino, 2-chloroanilino, diethylamine, dodecylamine; imino, such as 1-(N-phenylimido)ethyl, N-succinimido or 3-benzylhydantoinyl; phosphate, such as dimethylphosphate and ethylbutylphosphate; phosphite, such as diethyl and dihexylphosphite; a heterocyclic group, a heterocyclic oxy group or a heterocyclic thio group, each of which may be substituted and which contain a 3 to 7 membered heterocyclic ring composed of carbon atoms and at least one hetero atom selected from the group consisting of oxygen, nitrogen and sulfur, such as 2-furyl, 2-thienyl, 2-benzimidazolyloxy or 2-benzothiazolyloxy; quaternary ammonium, such as triethylammonium; and silyloxy, such as trimethylsilyloxy.

If desired, the substituents may themselves be further substituted one or more times with the described substituent groups. The particular substituents used may be selected by those skilled in the art to attain the desired photographic properties for a specific application and can include, for example, hydrophobic groups, solubilizing groups, blocking groups, and releasing or releasable groups. When a molecule may have two or more substituents, the substituents may be joined together to form a ring such as a fused ring unless otherwise provided. Generally, the above groups and substituents thereof may include those having up to 48 carbon atoms, typically 1 to 36 carbon atoms and usually less than 24 carbon atoms, but greater numbers are possible depending on the particular substituents selected.

The materials of the invention can be used in any of the ways and in any of the combinations known in the art. Typically, the invention materials are incorporated in a melt and coated as a layer described herein on a support to form part of a photographic element. When the term "associated" is employed, it signifies that a reactive compound is in or adjacent to a specified layer where, during processing, it is capable of reacting with other components.

To control the migration of various components, it may be desirable to include a high molecular weight hydrophobe or "ballast" group in

coupler molecules. Representative ballast groups include substituted or unsubstituted alkyl or aryl groups containing 8 to 48 carbon atoms.

Representative substituents on such groups include alkyl, aryl, alkoxy, aryloxy, alkylthio, hydroxy, halogen, alkoxycarbonyl, aryloxcarbonyl, carboxy, acyl, 5 acyloxy, amino, anilino, carbonamido, carbamoyl, alkylsulfonyl, arylsulfonyl, sulfonamido, and sulfamoyl groups wherein the substituents typically contain 1 to 42 carbon atoms. Such substituents can also be further substituted.

The entire contents of the patents and other publications referred to in this specification are incorporated herein by reference.